Sains Medika Journal of Medicine and Health
• pISSN: 2085-1545
• eISSN: 2339-093X
http://jurnal.unissula.ac.id/index.php/sainsmedika

RESEARCH ARTICLE

The Effect of Moderate-Intensity Physical Exercise on Interleukin-6 Level and Lymphocyte Count in Leprosy Reaction Patient

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ABSTRACT

Introduction: *Leprosy reaction is an immunity declining reaction marked with inflammation which may cause permanent disability. Physical exercise may improve body's immune system.* **Objective:** *To prove the effect of moderate-intensity physical exercise on the interleukin-6 level and lymphocyte count in leprosy reaction patient.*

Methods: *The quasi-experimental research with pretest and posttest and a control group design used 30 respondents consisting of 14 interventions and 16 controls. The intervention group was given moderate-intensity physical exercise 60%-79% in the form of static cycle at a frequency of 4 times weekly, 150 minutes per week. Corticosteroid was always administered to the two groups as a standard therapy. The interleukin-6 level was measured using ELISA method and lymphocyte count was measured using hematology analyzer.*

Result: *The Mann-Whitney analysis shows that the mean difference in IL-6 level between pretest and posttest with the intervention group (-7.1429±25.2369) is significantly lower than that of the control group (8.8125±11.2025), p<0.05. On the contrary, the Independent t-test analysis shows that the mean difference in lymphocyte count between pretest and posttest with the intervention group (0.7407±0.41236) is significantly higher than that of the control group (-0.4500±0.42415), p<0.05.*

Conclusion: *Physical exercise at moderate intensity in the form of aerobics using static cycle at a frequency of 4 times weekly, with duration of 150 minutes per week decreases interleukin-6 level and increases lymphocyte count in leprosy reaction patient.*

Keywords: *moderate-intensity exercise, IL-6, lymphocyte*

ABSTRAK

Latar belakang: Reaksi kusta merupakan reaksi penurunan imunitas ditandai adanya peradangan yang dapat menimbulkan kecacatan permanen. Latihan fisik dapat meningkatkan sistem imunitas tubuh. **Tujuan:** Membuktikan pengaruh latihan fisik intensitas sedang terhadap kadar interleukin-6 dan jumlah limfosit pada pasien reaksi kusta.

Metode: Penelitian *quasy experimental* dengan *pre and posttest with control group design*, menggunakan 30 responden yang terdiri dari 14 intervensi dan 16 kontrol. Kelompok intervensi diberikan latihan fisik intensitas sedang 60%-79% berupa static cycle, frekuensi 4 kali perminggu, waktu 150 menit perminggu Kortikosteroid tetap diberikan pada kedua kelompok karena merupakan terapi standard. Kadar interleukin-6 diukur dengan metode ELISA dan jumlah limfosit diukur dengan hematology analyzer.

Hasil: Analisis *Mann-Whitney* menunjukkan bahwa rerata selisih kadar IL-6 antara *pre* dan *postest* pada kelompok intervensi (-7,1429±25,2369) lebih rendah bermakna dibanding kontrol (8,8125±11,2025), p<0,05. Sebaliknya, analisis Independent *t-test* menunjukkan bahwa rerata selisih jumlah limfosit *pre* dan *posttest* pada intervensi (0,7407±0,41236) lebih tinggi bermakna dibanding kontrol (-0,4500±0,42415), p<0.05.

Kesimpulan: Pemberian latihan fisik dengan intensitas sedang berupa aerobik menggunakan *static cycle* dengan frekuensi latihan 4 kali perminggu, durasi waktu 150 menit perminggu berpengaruh terhadap penurunan kadar interleukin-6 dan meningkatkan jumlah limfosit pada pasien reaksi kusta.

Kata kunci: latihan intensitas sedang, IL-6, limfosit

INTRODUCTION

Leprosy reaction patients have their immunity declined as marked with inflammation on their skin and nerves, causing disability in the form of lagopthalmos, drop hand, claw hand, claw thumb, drop foot, ulcer and xerosis. Poor managed leprosy reaction will cause permanent disability. Leprosy reaction is treated using tapering off methyl prednisolone, but leprosy reaction may recur at a later date (Andini et al., 2016), due to declining level of immunity. Research shows that body's

immune system can be improved by doing physical exercise at moderate intensity such as gymnasium, load exercises, biking, jogging and others (Afriwandi, 2011; Noorhasanah, 2017; Bafirman and Wahyuri, 2018). Meanwhile, light- and high-intensity physical exercise cannot improve patient's immune level (Aroziah, Sugiharto & and Kinanti, 2014; Hayati, 2014). However, the effect of moderate-intensity physical exercise on leprosy reaction patient's immune level is still unclear.

Leprosy reaction is the main cause of disability in leprosy patient. Therefore, leprosy patients' disability rate is directly proportional to the rate of leprosy reaction occurrence. The rate of leprosy induced disability in Central Java is remain under standard. The rate of level 2 disability of people with leprosy in Central Java in 2017 was 0.53/100,000 population. The rate of disability level 2 of people with leprosy in Central Java in 2018 declined to 0.44/100,000 population. Meanwhile, the success indicator was (10%) <0.1/100,000 population (Prabowo, 2019). Moreover, the high rate of disability may affect the social and economic factors of leprosy patients.

A previous research shows the increased interleukin-6 on students who perform moderate-intensity physical exercise using multistage running test procedure of 20 meter shuttle test (Yuniarti, 2014). Lymphocyte count increases after moderate-intensity physical exercise in the form of swimming ranging from 80-90% from the time of exhausted condition with the laboratory rat (Shodiq, 2016). Another research also shows that moderate-intensity physical exercise in the form of gymnasium 4 times weekly or equally 60 minutes per week evidently increases lymphocyte count (Yasirin et al., 2014)(Yasirin et al., 2014). The researches show that moderate-intensity physical exercise for experimental animals and healthy humans may affect IL-6 level and lymphocyte count. However, further research is necessary to evaluate the effect of moderate-intensity physical exercise on people with leprosy.

Physical exercise work on hypothalamus to secrete corticotrophin releasing hormone (CRH) which then stimulates anterior hypophysis. Anterior hypophysis secretes endorphin which contributes to secretion of adrenocorticotropin hormone (ACTH) and cortisol (Fazio et al., 2008). The increase in hormones leads to decreased interleukin-6 (Wardhana, 2016). Interleukin-6 has many effects, for example on hepatocyte and lymphocyte, which may be detected in chronic inflammatory diseases such as in leprosy (Tanaka, Narazaki and Kishimoto, 2014). Furthermore, the body's main immunity component in blood circulation is lymphocyte, of which activity can be increased through physical exercise such as aerobics for 15-60 minutes 3-5 times weekly (Neil, 2011; Yasirin et al., 2014). Therefore, the research's objective was to evaluate the effect of physical exercise at moderate intensity on the decline in interleukin-6 level and increase in lymphocyte count. Decreased interleukin-6 level and increased lymphocyte count are expected to decrease leprosy reaction recurrence.

METHODS

This quasi-experimental research employed a nonequivalent control group approach to examine the influence of moderate-intensity physical exercise on the decrease in interleukin-6 level and increase in lymphocyte count in leprosy reaction patients (Riyanto, 2011). The research population was all patients diagnosed with leprosy reaction, both outpatients and inpatients of RSUD Kelet. The subjects were sampled using nonprobability (nonrandom) with total sampling technique. The research subject who meets the inclusion criteria of about 30 people, divided into 2 groups, namely 14 people of intervention group and 16 people of control group. Both the intervention and control groups received medical treatment and measures in accordance with the hospital's procedures of administration of methyl prednisolone by tapering off, while the intervention group was administered with intervention of moderate-intensity physical exercise 4 times weekly, 150 minutes per week, for 2 weeks. The physical exercise was aerobics performed with static cycle (warming up 5 minutes, core exercise 37.5 minutes, cooling down 5 minutes). The research was conducted under approval of the Ethical Committee of the Medical Faculty, UNISSULA no.222/VII/2020/ Komisi Bioetik.

How to Measure Physical Exercise

The intensity of physical exercise was categorized into five levels (Purwanto, 2011; Budiwanto, 2012), namely: extremely light (≤ 35 %), light (35 - 59 %), moderate (60% - 79%), high (80% - 89%), and extremely high (≥90%). This research employed moderate intensity 60-70%.

Before exercise, the heartbeat was first counted using Karnoven formula (Saputra & Arifin, 2019) as follows:

1 Measuring resting heart rate (RHR)
2 Measuring estimated maximum heartbeat
HRmax (male) = 220-age
HRmax (female) = 226-age

Table 1. Basic Characteristics of Leprosy Patients

Characteristics	Groups	
	Intervention	Control
Total	14	16
Age	38.64±15.56	39.38±14.30
Gender		
Male	13(92.9%)	9(56.2%)
Female	1(7.1%)	7(43.8%)
Reaction Type		
Type 1	0 (0%)	0 (0%)
Type 2	14 (100%)	16 (100%)
RFT Status		
After RFT	11 (78.6%)	9 (56.2%)
before RFT	3 (21.4%)	7 (43.8%)
IL-6 level	68.07±12.517	68.06±11.180
Lymphocyte count	1.30±0.59053	1.31±0.38505

Table 2. Analysis Result of mean Interleukin-6 level and lymphocyte count in the Pretest and Posttest of both Intervention Group and Control Group

Variables	Groups					
	Intervention (N=14)			Control (N2=16)		
	Pre test $\chi \pm$ (SD)	Post test $\chi\pm$ (SD)	Dif const (δ)	Pre test $\chi\pm$ (SD)	Post test $\chi\pm$ (SD)	Dif const (δ)
IL-6 level (pg/mL)	68.07 ±12.51	60.93; ±18.64	-7.14; ±25,23	68.06; ±11.18	76.88; ±10.97	8.81; ±11.20
Lymphocyte count (Σ)	1.30; ±0.59	2.04; ±0.71	0,74; ±0.42	1.31; ±0.38	0.86; ±0.25	-0.45; ±0.43

3 Measuring heart rate reserve (HRR)
HRR=HRmax–RHR
4 Measuring THR min
THRmin = (HRR x lower intensity%) + RHR
5 Measuring THRmax
THRmax=(HRRx upper intensity%)+HR
Heart rate (HR) was measured using pulse oximeter

Measuring Interleukin-6 Level

Interleukin-6 level was measured from the pre- and post-treated blood sample (intervention and control groups). The blood was taken from median cubital vein for 2 cc. Plain/red Vaculab blood tube (serum) for interleukin-6 level examination was centrifuged at 3000 rpm for 10 minutes to separate serum from other parts of blood. The serum was then immediately stored at -200 C. The interleukin-6 level was then examined using ELISA method.

Measuring Lymphocyte Count

Lymphocyte count was measured from the pre- and post-treated blood sample (intervention and control groups). The blood sample was taken from median cubital vein for 1 cc, EDTA vacutainer/purple blood tube for lymphocyte count examination. The lymphocyte count was examined using hematology analyzer.

Statistical Analysis

The statistical analysis for pretest and posttest interleukin-6 level employed Mann-Whitney test (the data were not normally distributed), and pair t test was employed for pretest and posttest lymphocyte count (the data were normally distributed). The analysis on posttest interleukin-6 level for intervention group and control group employed Wilcoxon test, and independent t test for was employed for lymphocyte count. The analysis result was deemed significant if $p<0.05$.

RESULTS

The research subject's basic characteristics before moderate-intensity physical exercise for two weeks are presented in table 1 below.

After the research was conducted, the result is presented in table 2 below.

The result of this research shows reduction in pretest and posttest mean IL-6 level with the intervention group from 68.07 to 60.93, while the control group has an increment in IL-6 level from 68.06 to 76.88. However,

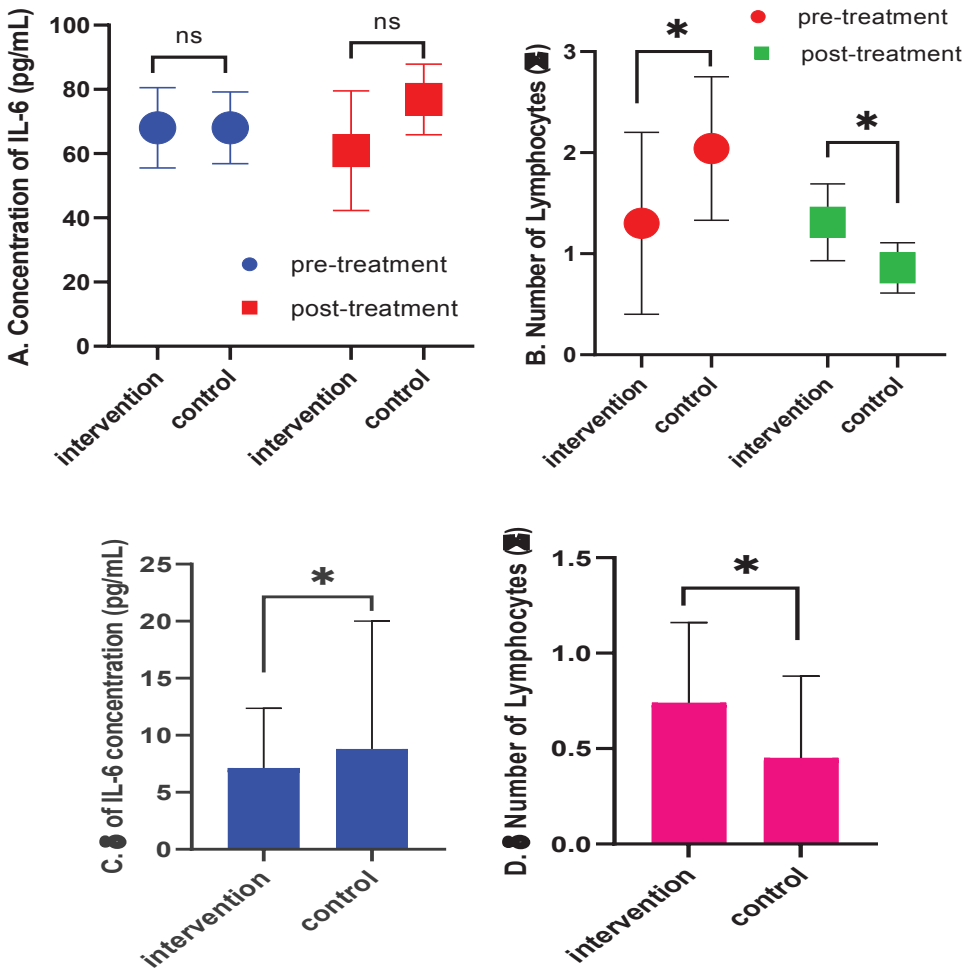

Figure 1. Concentration of IL-6 and number of lymphocytes in each group. A. the difference concentration of IL-6; B. The difference number of lymphocytes; C. The difference oconcentration of IL-6; D. The difference number of lymphocytes. Statistical analysis: * p<0.05; ns: not significant.

the result of Wilcoxon test does not show any significant difference in the IL-6 level reduction of the intervention group or the IL-6 level increment of the control group, each with p value>0.05 (figure 1).

On the other hand, the intervention group has its mean lymphocyte count increased from 1.30 to 2.04, while the control group has its mean lymphocyte count decreased from 1.31 to 0.86. The result of paired sample t-test shows significant difference both in the intervention group and control group, p<0.05 (figure 1).

Furthermore, to evaluate whether there is different influence on intervention group and control group regarding interleukin-6 level and lymphocyte count, it is necessary to conduct a statistical test on the mean difference in the change to IL-6 level and lymphocyte count in the intervention and control groups. The result of Mann-Whitney test shows that the interleukin-6 level of the intervention group is significantly lower than that of the control group, p<0.05. The result of independent sample t-test on lymphocyte count shows that the lymphocyte count of the intervention group is significantly higher than that of the control group, p<0.05 (figure 1).

DISCUSSION

The result shows that moderate-intensity physical exercise for people with leprosy reaction shows a significant decrease in the difference value of pretest and posttest (δ) interleukin-6 level of the intervention and control groups. This explains that moderate-intensity physical exercise is able to reduce IL-6 level. IL-6 level decreases in the intervention group and increases in the control group. The research result is different from the result of research conducted by Cornish and Johnson, which explains that there is no significant increase in IL-6 level after intervention in the form of knee flexion exercise (Cornish and

Johnson, 2014). The study conducted by Bongga also shows no significant difference in IL-6 level on futsal at night (Bongga, 2018)(Bongga, 2018). According to Berawi, physical exercise with duration from 90 to 120 minutes may stimulate formation of free radicals because of increased oxidative stress. Oxidative stress is closely related to apoptosis, vasoconstriction, systemic inflammatory process, and endothelial cell proliferation (Berawi and Agverianti, 2017).

Based on this research result, the body's immunity of leprosy reaction patient can be improved through moderate-intensity physical exercise as per recommendation from the American Heart Association (AHA) of 150 minutes/week. Moderate-intensity physical exercise affect hypothalamus that can release corticotropin realizing hormone (CRH), which then sends message to pituitary. Pituitary will release endorphin hormone, leading to a decrease in interleukin-6, while interleukin-2 and interleukin-4 does not increase (Wibowo et al., 2016). In addition, endorphin can also increase physical fitness and IgG. Moreover, increased endorphin because of moderate-intensity physical exercise also relax the mind and soften the emotion. Appropriate continuous physical exercise can reduce oxidative stress through 3 mechanisms (Candrawati, 2013), namely: (1) increasing proteasomes and DNA repairing enzymes, (2) reducing DNA bond with NF-κB, AP-1, MAPK, and CREB and (3) increasing superoxide dismutase (SOD) and glutathione peroxidase (GPx).

Normally, interleukin-6 is strictly regulated and expressed in a very small quantity, except in a chronic infection condition such as leprosy reaction or trauma, thus the IL-6 in the control group is increased. The inflammatory role of IL-6 occurs in acute inflammatory process marked with Th2. On the contrary, the proinflammatory role of IL-6 occurs in chronic process, such as leprosy (Tanaka, Narazaki and Kishimoto, 2014; Vionni, Arifputra and Arifputra, 2016; Kang et al., 2019). In leprosy reaction type 2, the focus of acute inflammation on tissue in the form of erythema nodosum is caused by increased serum IFN-γ, TGF-β, interleukin-10, interleukin-6 and interleukin-8 and interleukin-1B, while interleukin-4, and interleukin-5 does not change. Non-detected leprosy reaction condition may cause disability (Aditama, 2012; Hamzah et al., 2018).

Mean difference value of pretest and posttest lymphocyte counts between the intervention and control groups, shows intervention affect lymphocyte count. This result is in line with some previous researches, such as that conducted by Shodiq, which states that moderate-intensity physical exercise in the form of swimming may increase the lymphocyte count of laboratory rat (Shodiq, 2016). The study conducted by Yasirin states an increase in lymphocyte count with moderate-intensity physical exercise in the form of aerobics (Yasirin et al., 2014). These researches are conducted on healthy humans and experimental animals, but not on people with leprosy. Meanwhile, this research is conducted on leprosy reaction patients, showing that moderate-intensity physical exercise can improve lymphocyte count.

The effect of physical exercise on an increase in lymphocyte count can also be caused by some factors, such as catecholamine mediation, cortisol, demargination, neuron transmitters and peptide or purine chemical transmitters. Physical exercise can increase lymphocyte count because of the large amount of lymphocytes entering into vascular endothelium by diapedesis through blood circulation. Continuous physical exercise causes a change to the lymphocyte movement characteristics to fight and locate infection (Sandy et al., 2019).

Lymphocyte T helper, by type of cytokine produced, is divided into Th1 or proinflammatory cytokines TNF-α, TNF-β, IFN-γ, also called lymphotoxin (LT), while ones serving to activate cellular immunity and non-specific immunity are IL-12, IL-8, IL-6, IL-1. Th2 produces anti-inflammatory cytokines IL-4 and interleukin-10 which serve to activate humoral immunity (Harapan et al., 2018). The trans-membrane complexes of weak affinity, namely T-cell antigen receptor (TCR), can be used by lymphocyte T to recognize various antigens. T-cell MHC class I and MHC class II can recognize antigen. Co-receptor CD4 or CD8 is part of T-cell. Proliferation and distinguishing signal are part of CD4+ T-cell's tasks. T-cell may control intracellular antigen such as leprosy bacteria and fungi (Sudiono, 2014).

Lymphocyte count decreases in control group, commonly with patients having infection/inflammation and the influence of long-term administration of corticosteroid. Some effects of the use of methyl prednisolone include: (1) decreased lymphocyte count and peripheral monocyte count within 4 hours because of temporary redistribution of lymphocyte from intravascular into lymph node, lymph, thoracic duct and bone marrow, (2) decreasing process of fibroblast formation, and (3) decreased movement count and leukocyte functions (Hidayanti, Astuti and Kustyawati, 2014). Patients administered with methyl prednisolone were evaluated once every 14 days with nerve function examination and recorded on leprosy reaction treatment evaluation form, that if the condition gets better, the

dose was reduced, but in case of no improvement, the dose was maintained, and if it worsen, the dose was increased (Riyanto, 2011).

Moderate-intensity physical exercise influences a decrease in IL-6 level and an increase in lymphocyte count and will reduce reaction recurrence. If leprosy reaction is not well managed, it may cause permanent disability. Leprous disability inflicts negative medical impact and also influences social, economic and psychological issues. Disabled leprosy patient will receive negative stigma, discrimination and tend to have their working productivity lost. Comprehensive management of leprosy from promotional, preventive, curative to rehabilitative activities is indispensable for minimizing the problems (Riyanto, 2011).

CONCLUSION

Moderate-intensity physical exercise in the form of aerobics using static cycle at a frequency of 4 times weekly, with duration of 150 minutes per week significantly decreases interleukin-6 level and increases lymphocyte count in leprosy reaction patient.

ACKNOWLEDGMENT

We would like to give our greatest appreciation and gratitude to the Integrated Biomedic Laboratory, Medical Faculty, Sultan Agung Islamic University of Semarang (Universitas Islam Sultan Agung Semarang), and Laboratory of Regional Public Hospital Kelet, Central Java for their cooperation in this research.

CONFLICT OF INTEREST

There is no conflict of interest in this publication.

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